REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	1990	Reprint

4. TITLE AND SUBTITLE

(see title on reprint)

5. FUNDING NUMBERS

Program Element No.
NWED QAXM

Work Unit No.
00107, B3131, B5137

6. AUTHOR(S)

Zeman et al.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Armed Forces Radiobiology Research Institute
Defense Nuclear Agency
Bethesda, MD 20889-5145

8. PERFORMING ORGANIZATION REPORT NUMBER

SR90-10

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Defense Nuclear Agency
Washington, DC 20305

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS

15. NUMBER OF PAGES
9

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED		

RADIATION RESEARCH 121, 54-62 (1990)

Nonuniform Irradiation of the Canine Intestine.

II. Dosimetry

G. H. ZEMAN,[1] T. H. MOHAUPT,[2] P. L. TAYLOR,[3] T. J. MACVITTIE, A. DUBOIS,* AND R. M. VIGNEULLE

*Armed Forces Radiobiology Research Institute, and *Uniformed Services University of Health Sciences, Bethesda, Maryland 20814-5145*

ZEMAN, G. H., MOHAUPT, T. H., TAYLOR, P. L., MACVITTIE, T. J., DUBOIS, A., AND VIGNEULLE, R. M. Nonuniform Irradiation of the Canine Intestine. II. Dosimetry. *Radiat. Res.* 121, 54-62 (1990).

An experimental model has been developed for quantitative studies of radiobiological damage to the canine small intestine following partial-body nonuniform irradiation. Animals were irradiated with ^{60}Co γ rays to simulate the nonuniform irradiation which do occur in victims of radiation accidents. The model used a short source-to-surface distance for unilateral irradiations to produce a dose gradient of a factor of two laterally across the canine intestinal region. The remainder of the animal's body was shielded to prevent lethal damage to the bone marrow. *In situ* dosimetry measurements were made using thermoluminescent dosimeters to determine the radiation dose delivered as a function of position along a segment of the small intestine. This system made it possible to correlate the radiation dose delivered at a specific point along the small intestine with the macroscopic and microscopic appearance of the intestinal mucosa at that point, as determined by direct observation and biopsy using a fiberoptic endoscope. A key feature of this model is that dosimetry data for multiple sites, which receive a graded range of radiation doses, can be correlated with biological measurements to obtain a dose–response curve. This model is being used to evaluate the efficacy of new therapeutic procedures to improve survival following nonuniform irradiation.

INTRODUCTION

Central to the prediction of the outcome of highly nonuniform or partial-body irradiation is accurate assessment of the injury after either accidental or therapeutic exposures. In the documented accidents involving fatal irradiation of humans, most victims received highly nonuniform doses (*1*). Nevertheless, current knowledge of the biomedical effects of nuclear radiation is based largely on studies using uniform exposures. Standards of dose uniformity for radiobiology research, defined by the International Commission on Radiation Units and Measurements (*2*), specify no more th 0% dose variation across an animal for "uniform" irradiation and no more than 30% variation for "moderately uniform." The 10% uniformity criterion is readily achieved in most small animal studies. The moderately uniform criterion is possible with many larger animal irradiations if multilateral exposure is used or if the experimental subject is rotated.

This paper describes our efforts to develop a method to determine radiation dose deposition along the intestinal tract more accurately following nonuniform localized irradiation. One critical component of the experiment is the use of a large animal model (canine) so that a highly nonuniform dose will be distributed acrc GI tract; this is essential if analogy is to be made to h adiation exposures. A second component of the ex it is the use of *in situ* dosimetry which, along with endoscopy and tissue biopsies of the small intestine, makes site-specific studies of radiation damage along the length of the intact intestine possible.

MATERIALS AND METHODS

Inserting a dosimetry tube or an endoscope into the small intestine, either through the nasogastric route or through the rectum, poses severe logistical complications. To sidestep these complications, a continent ileostomy was created to provide a direct access to the ileum that does not interfere with transit through the small intestine. This procedure utilizes a modified "Roux-en-Y" surgical preparation which is described in detail in the companion paper (*4*).

In vivo dosimetry was done using Harshaw (Solon, Ohio) TLD-100 lithium fluoride thermoluminescent dosimeter chips (TLDs) encased in gelatin capsules with tissue-equivalent plastic filling the gaps. Three TLDs were loaded into each capsule to provide replicate measurements. Two separate dosimetry tubes were developed (Fig. 1). The first contained 30 TLD capsules loaded in a 90-cm length of Tygon tubing. By making dose measurements every 3 cm, it was assured that no two adjacent measurements would differ by more than 20% and no sizable interpolations would be required. Later, a second 90-cm tube was loaded with only 15 TLD capsules because our experience with the first tube indicated that dose measurements every 5 to 6 cm were adequate to define the dose profile along the length of the intestine.

Nylon spheres and a capsule of lead (Pb) beads were positioned between adjacent dosimetry capsules in each Tygon dosimetry tube. The capsule

[1] Present address: AT&T Bell Laboratories, 600 Mountain Avenue, Murray Hill, NJ 07974-2070.

[2] Present address: Great Lakes Naval Hospital, Great Lakes, IL 60088.

[3] Present address: Department of Radiation Medicine, Georgetown University Hospital, 3800 Reservoir Road N.W., Washington, DC 20007.

0033-7587/90 $3.00

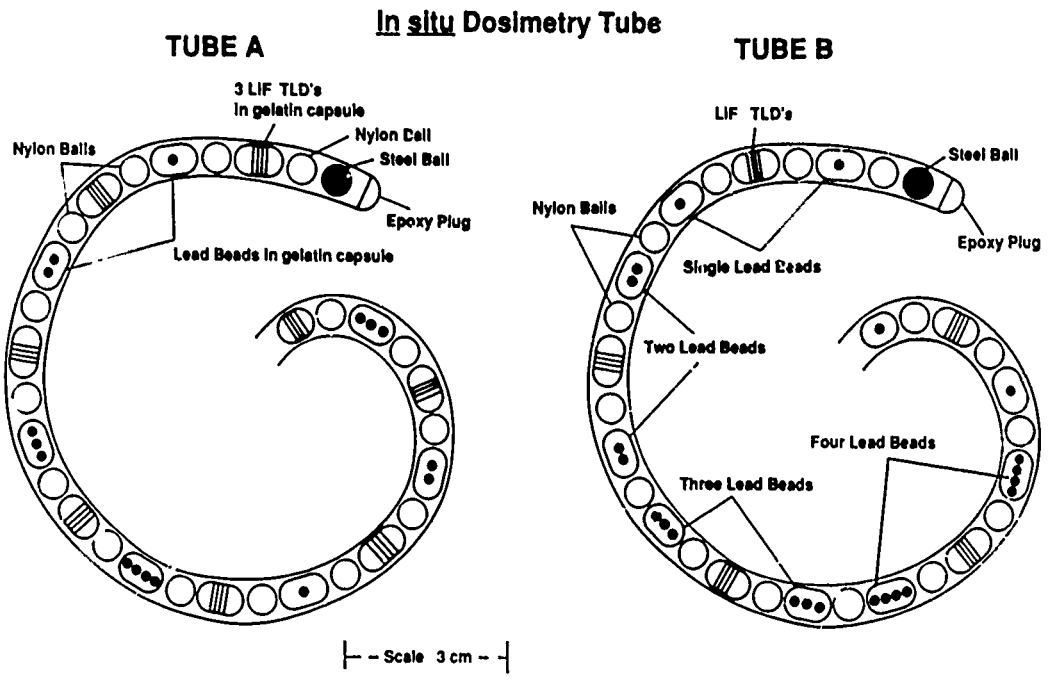

FIG. 1. Dosimetry tubes used for *in vivo* TLD measurements. Tube A was used for high resolution measurements, with a TLD group positioned every 3 cm. In tube B the distance between TLD groups was 6 cm. The distinct lead marker sequences in each tube facilitated TLD localizations on radiographs.

with Pb beads had one, two, three, or four beads epoxied in place to prevent movement. The capsules were spaced sequentially in the Tygon tube to identify locations on orthogonal radiographs taken before and, in some cases, after irradiation. A Pb solder marker was also used to locate the exit end of the tube on the radiographs. The nylon spheres were used as spacers to separate the TLD capsules from those containing Pb beads, thereby preventing any local shielding effects.

The leading end of each dosimetry tube was identified by a unique steel bead. To facilitate passage of the tube through the intestinal lumen, the leading end was sealed with epoxy to a smooth rounded finish and lubricated. The dosimetry tube was flexible and easily followed the tortuous path of the small intestine.

After exposure the TLDs were read on either a Harshaw Automatic Reader Model 2000D or a Harshaw TL Analyzer Model 2080. Each batch of TLDs was calibrated with a Theratron-80 ^{60}Co beam with exposure rate calibration traceable to the National Institute of Standards and Technology. Individual TLDs within each batch varied in sensitivity by a standard deviation of the mean response of the TLDs of approximately 4%. For each batch, five sets of four TLDs were irradiated to develop a calibration function (Fig. 2) to correlate TLD response to absorbed dose.

After the dosimetry tube was inserted into the canine's ileum and secured to prevent slippage, the point on the tube where it exited the stoma was marked for reference. The animal was placed in an acrylic restraint box with sides 6 mm thick. The locations of the lead beads were documented on orthogonal radiographs made using a diagnostic X-ray machine (see Results). The course of the dosimetry tube within the animal was determined from the sequence of Pb beads on the resulting films.

Canines were unilaterally irradiated in the Armed Forces Radiobiology Research Institute (AFRRI) Whole Body ^{60}Co Irradiation Facility (Fig. 3). The distance between the ^{60}Co source and the canine midline was 118 cm. At this distance a dose gradient of a factor of two across the animal was expected on the basis of computer-generated isodose curves for a cylindrical water phantom (Fig. 4). Preirradiation dosimetry measurements were made each day using AFRRI 50 cm^3 spherical ionization chambers. The midline dose rate was nominally 3.8 Gy/min based on a midline tissue-to-air ratio of 0.90 applicable for a nominal diameter of 12.6 cm (6). Dose delivery was verified by TLDs irradiated on the entrance and exit surfaces of each animal. Results shown in Table I indicate a remarkably constant

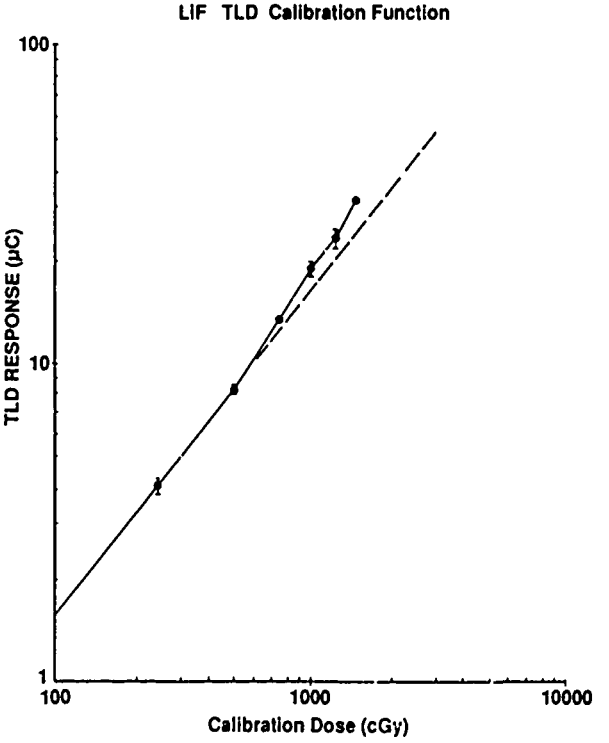

FIG. 2. Calibration curve for TLDs. Each point represents the average of four TLDs. The doses measured in this study of GI damage fall in the range where significant LiF supralinearity occurs. Separate calibration curves were run for each new set of experiments. Error bars represent 1 SD.

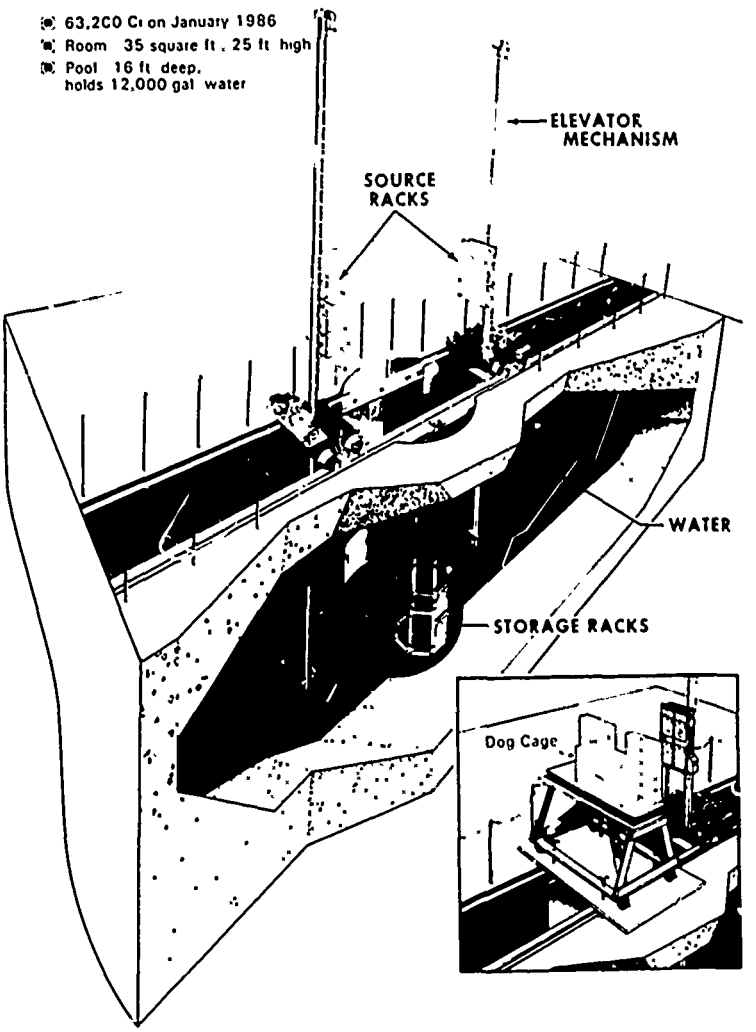

FIG. 3. ^{60}Co Whole Body Irradiation Facility. The main figure shows the facility configuration for routine bilateral exposure (5). The inset shows the unilateral irradiation arrangement used in the experiments reported here. The 5-cm-thick Pb bricks shielded the pelvis, spine, and other bones to minimize hematopoietic radiation damage.

ratio (average = 2.12:1) between entrance and exit doses in the first series of animals irradiated in these experiments.

Partial body shielding was provided for each canine by using 5-cm-thick Pb bricks to restrict the radiation field to the area of the intestinal tract (inset, Fig. 3). The resulting ^{60}Co beam exposing the canine gut was approximately 24 cm (width) × 40 cm. The 5-cm bricks attenuated the ^{60}Co intensity by a factor of over 90%. Because of scatter and penumbra effects at the edges of the shields, the dose to some regions of the spine and pelvis was 7 to 10% of the dose at the midline of the open field; other regions of bone marrow received doses less than 7% of nominal midline dose. This shielding was sufficient to allow evaluation of direct GI radiation damage without the influence of concurrent lethal damage to the blood-forming organs.

RESULTS

This *in vivo* TLD dosimetry system allowed measurement of the ^{60}Co dose deposited in the canine small intestine at known distances from the ileostomy. Figure 5 shows dorsal–ventral radiographs of dosimetry tubes in canines just prior to irradiation. Figure 6 shows lateral radiographs of the same animals. The path of the dosimetry tubes is enhanced in each image to show its course through the intestine. It is clear that the position of any specific site along the small intestine is unique for each animal. These radiographs indicate that the radiation dose delivered to specific sites along the intestine cannot be predicted on the basis of external dosimetry measurements or calculations. Only by *in vivo* measurements was it possible to specify the dose for anatomical correlation with endoscopy or other measures of biological damage.

Figure 7 shows the measured ^{60}Co dose as a function of distance from the stoma in the same animals seen in Figs. 5 and 6. The dose was determined from the median TLD reading in each group, with error bars indicating the range. The measured dose profiles varied by a factor of almost two; these variations were in general agreement with the lateral depth of penetration as judged from the dorsal–ventral ra-

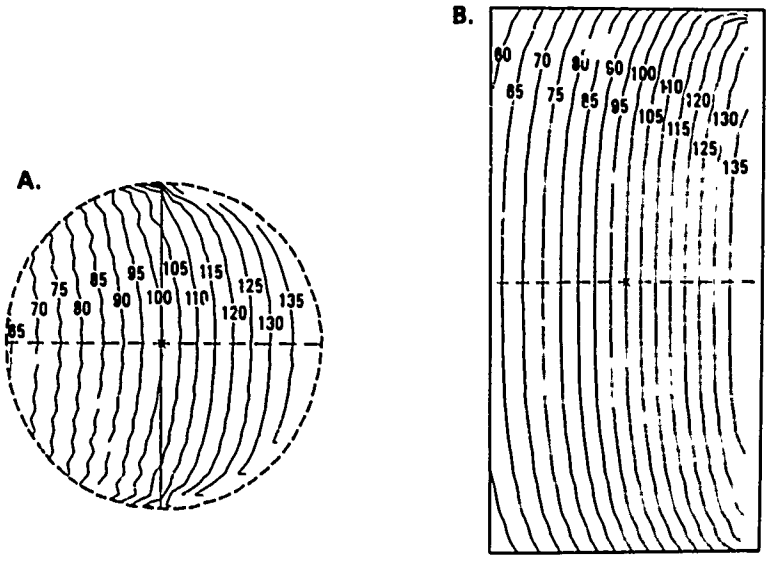

FIG. 4. Calculated ^{60}Co isodose distributions in a cylindrical water phantom. Numerical values give the radiation dose as a percentage of the midline dose. Calculations were for a 15-cm-diameter phantom 32 cm in length.

diographs. However, an exact correlation of dose with depth was not expected, on the basis of the variable heights of the TLD locations as judged from the lateral radiographs. More precise correlations would require a three-dimensional localization of the dosimeters and a three-dimensional outline of each animal. Fortunately the ^{60}Co radiation doses measured by the *in vivo* thermoluminescent dosimetry tube can provide all the information required for radiobiological studies along the length of the intestine.

TABLE I
Entrance–Exit Dosimetry for Canines Unilaterally Irradiated with ^{60}Co

Animal no.	Nominal dose (Gy)	Entrance dose (Gy)	Exit dose (Gy)	Entrance to exit ratio	Weight (kg)
1	10.00	12.38	5.61	2.21	13.3
2	10.00	12.05	5.32	2.27	14.4
3	10.00	12.05	6.45	1.87	12.7
4	10.00	12.65	6.37	1.99	11.6
5	10.00	12.63	6.04	2.09	14.6
6	10.00	12.30	6.14	2.00	14.2
7	10.00	12.34	5.89	2.10	14.2
8	10.00	12.77	6.22	2.05	12.7
9	10.00	13.34	5.96	2.24	11.3
10	10.00	12.42	5.56	2.23	14.6
11	10.00	12.89	6.20	2.08	13.8
12	10.00	12.75	6.37	2.00	9.7
13	10.00	12.53	5.94	2.11	11.3
14	10.00	12.16	6.02	2.02	12.7
15	10.00	12.14	5.78	2.19	12.4
16	10.00	11.53	5.71	2.02	15.1
17	10.00	11.02	4.16	2.65	14.2
18	10.00	12.35	5.71	2.16	12.7
19	15.00	17.10	8.25	2.07	15.2
20	15.00	17.88	8.79	2.03	15.7

Note. Average ratio, 2.12; standard deviation ±7%.

Figure 8 shows the relationship between the average of the radiation doses measured by the TLDs within the intestine of each animal and the nominal or midline doses delivered to that animal. Each point in Fig. 8 represents results for a single animal. The data show that the measured dosimetry results are dispersed within a band ±20% above and below the nominal doses. These results imply that the nominal or midline dose does not characterize the average absorbed dose within the intestine precisely.

In several animals for which both pre- and postirradiation radiographs were made, changes in the position of the small intestine were observed (see Fig. 9). These changes were attributed either to the handling of the canine's restraint box during transport to and from the irradiation facility or to the natural movement of the unanesthetized animal within the restraint box. However, the TLDs were in place *in vivo* during the time of irradiation, so the measured doses accurately reflect the absorbed dose to the intestinal wall at the known distances from the stoma. Movement of the intestines before or after irradiation does not affect the accuracy of the dosimetry results or of the dose-location correlations.

It was also observed that if a dosimetry tube was removed and then reinserted, the final path followed by the small intestine differed appreciably from the original path. This finding emphasized the transient path and location of specific sites along the small intestine.

To correlate dosimetric and endoscopic results reliably, it was necessary to assume that the small intestine did not stretch unreasonably during sequential insertions of the endoscope or the dosimetry tube. The validity of this assump-

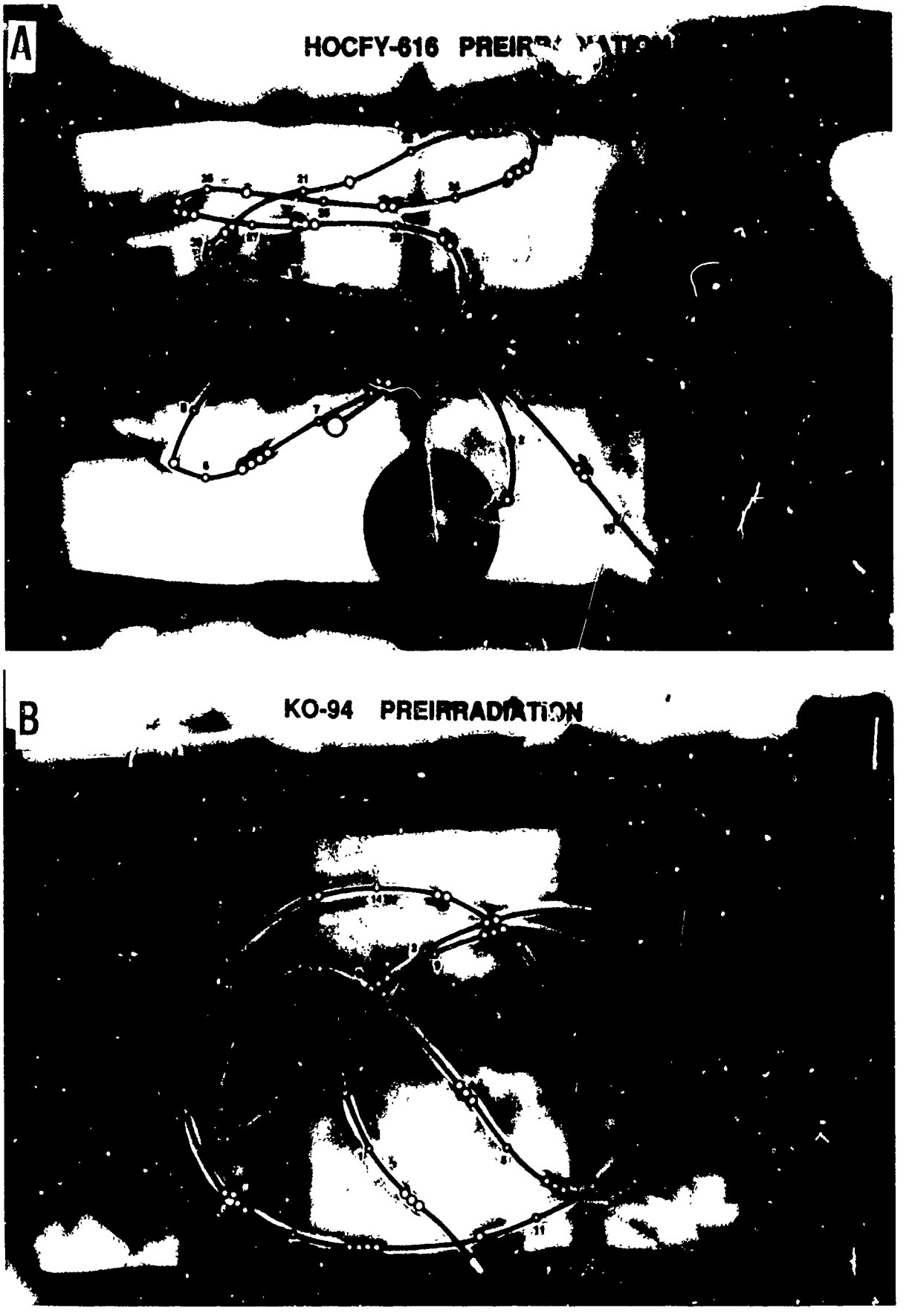

FIG. 5. Dorsal-ventral radiographs of the *in vivo* dosimetry tube in two different animals. The dosimetry tube has been highlighted to accentuate its path within the intestine. Numbers along the paths of the tubes refer to TLD locations, see Fig. 8 for corresponding radiation dose values.

FIG. 6. Lateral radiographs of the *in vivo* dosimetry tube in two different animals. See Fig. 5 for details.

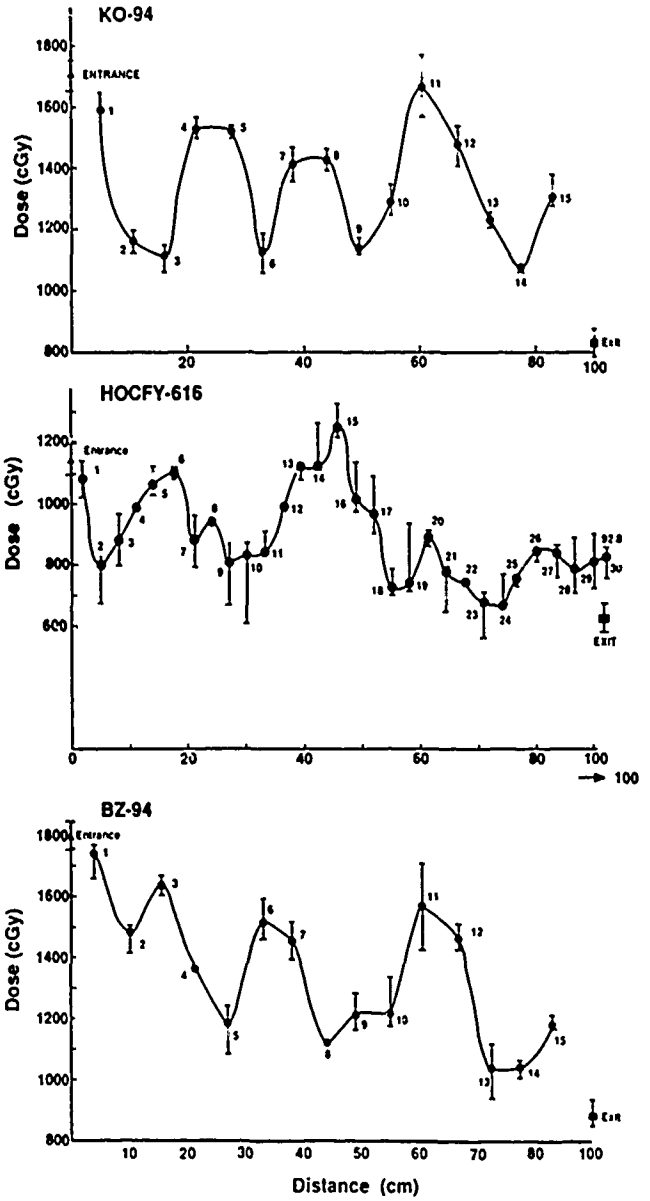

FIG. 7. Measured radiation doses along the length of the dosimetry tube for three different animals. The distance scale refers to distance along the path of each dosimetry tube. The entrance and exit doses plotted on each graph refer to measurements made with separate TLDs positioned on the external surfaces of each animal. Error bars represent range of data.

tion was tested in a control animal by means of fluoroscopy. The endoscopy tube was inserted (nominally 30 cm) until it reached the only reproducible landmark available, namely the surgical anastomosis, and the exact distance was noted. After the endoscopy tube was removed, the dosimetry tube was inserted an equal distance into the intestine. A thin tube filled with radio-opaque fluid was attached to the dosimetry tube to determine its location. Injection of the fluid was observed under fluoroscopy to result in a split stream, simultaneously entering both branches of the anastomosis. It was concluded from this observation that equal reinsertion of the tubes resulted in equal positioning without significant stretching of the intestine.

Endoscopic examinations were performed by inserting the endoscope to depths where dosimetry measurements had been made. The examinations consisted of visualization of the small intestine as well as tissue biopsies for cultures and further analyses as reported in the companion paper (*4*).

DISCUSSION

The experimental model described in this paper facilitates quantitative studies of radiobiological damage to the small intestine following partial-body nonuniform irradiation. The model may be used to obtain intraintestinal dosimetry results from a living animal, and biological observations and samples from specific intestinal sites may be taken at any time before and after irradiation. Thus each animal serves as its own control and provides a complete time course of radiobiological damage and repair. *In vivo* dose measurements make it possible to specify the absorbed dose precisely at locations along the nonuniformly irradiated small intestine. The nonuniform irradiation assures that the absorbed radiation dose varies by a factor of roughly two through regions of the small intestine in each animal. Biological samples from specific locations within the intestine may be directly correlated with the associated radiation dose.

The dosimetry studies reported here emphasize that the movement of the small intestine varies greatly from animal to animal; within an animal, the intestine was also found to change location. A reasonable correlation was generally

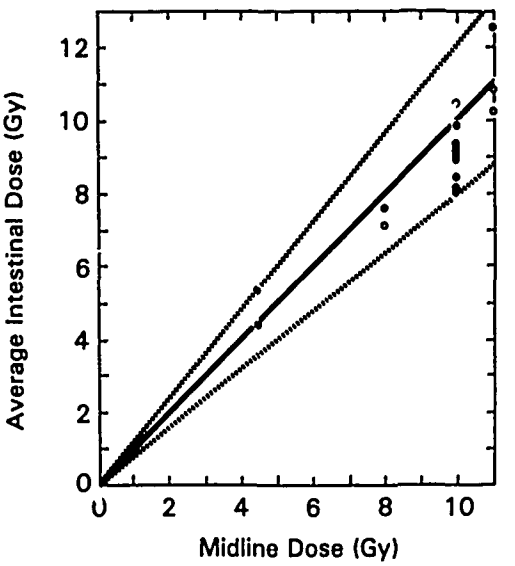

FIG. 8. Correlation of average canine intestinal dose with midline dose. Each point represents the average of all TLD readings from an individual animal. The dashed lines show a ±20% response range above and below the midline dose.

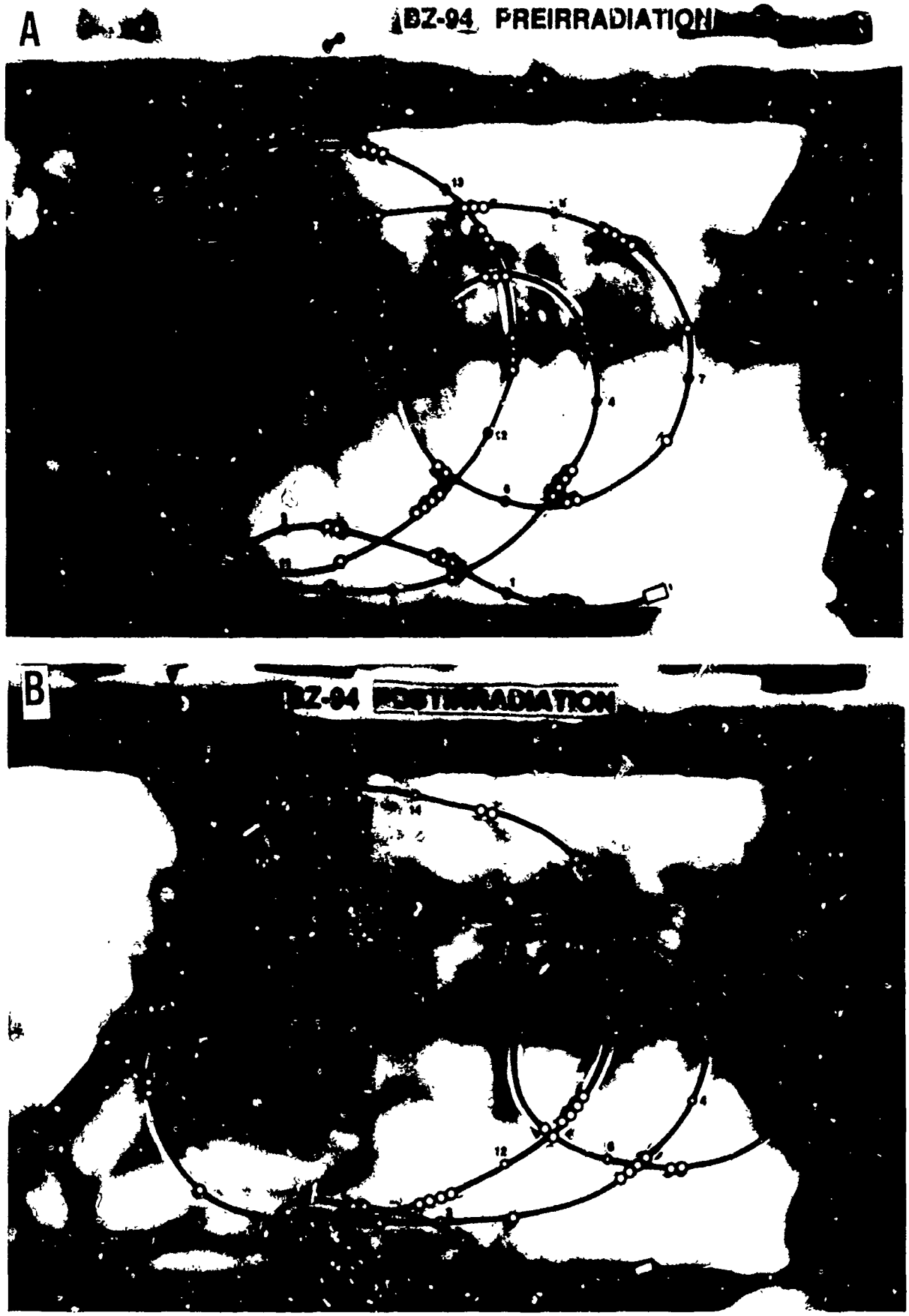

FIG 9 Pre- and postirradiation dorsal-ventral radiographs of the same animal showing the changed configuration of the dosimetry tube (e.g., note the different locations of the round marker on the distal end of the tube).

observed between measured dose distributions and anticipated doses based on radiographic positions of the dosimeters. However, these comparisons were complicated by the possible movement of the intestine (and the dosimeters) between the time of irradiation and recording of the radiograph and by the actual three-dimensional location of the dosimeters relative to the animal's surface contour. The above observations are consistent with the broad variability (±20%) observed between each animal's average TLD dose and the value of the nominal midline radiation dose. This variability implies that radiosensitive regions of the intestine may be more or less heavily irradiated in individual animals depending on the precise location of the intestine within each animal at the time of irradiation. These findings made it clear that external dosimetry measurements or calculations cannot reliably predict the radiation dose at specific sites along the small intestine.

It was demonstrated that the elastic properties of the small intestine were such that sequential penetrations of the ileostomy at equal distances caused the dosimetry tube or endoscope to reach the same location within the intestine. This reproducibility was essential to efforts to correlate measured radiation doses with subsequent endoscopic findings and to assure that sequential samples are taken from the same site at the different times after irradiation.

Extension of the dosimetry techniques described in this paper could be applied to other large animals or to other radiation sources. This ability to describe quantitatively the radiation dose deposition and radiobiological damage along the length of the intestine is being used in the evaluation of new therapeutic procedures to improve survival following nonuniform irradiation.

ACKNOWLEDGMENTS

This research was supported by the Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, under Work Units 107, B3131, and B5137. The opinions and assertions contained herein are those of the authors; no endorsement by the Defense Nuclear Agency has been given or should be inferred. The experiments reported herein were conducted according to the principles set forth in the "Guide of the Care and Use of Laboratory Animals," Institute of Animal Resources, National Research Council, DHEW Publication No. (NIH) 78-2.

RECEIVED: March 27, 1989; ACCEPTED: August 8, 1989

REFERENCES

1 K. F. BAVERSTOCK and P. J. N. D. ASH, A review of radiation accidents involving whole body exposure and the relevance to the $LD_{50/60}$ for man. *Br J Radiol.* **56**, 837-849 (1983).

2 ICRU, *Quantitative Concepts and Dosimetry in Radiobiology*, Report 30. International Commission on Radiation Units and Measurements, Washington, DC, 1979.

3 J. ZOETELIEF, L. A. HENNEN, and J. J. BROERSE, Some practical aspects and dose specification for the whole body irradiation. In *Response of Different Species to Total Body Irradiation* (J. J. Broerse and T. J. MacVittie, Eds.). Nijhoff, Dordrecht, The Netherlands, 1984.

4 R. M. VIGNEULLE, J. HERRERA, T. GAGE, T. J. MACVITTIE, P. L. TAYLOR, G. H. ZEMAN, J. B. NOLD, and A. DUBOIS, Nonuniform irradiation of the canine intestine. I. Effects. *Radiat. Res* **121**, 46-53 (1990).

5 R. E. CARTER and D. M. VERRELLI, *AFRRI Cobalt Whole-body Irradiator*, Technical Repor TR 73-3. Armed Forces Radiobiology Research Institute, Bethesda, MD, 1973.

6 G. H. ZEMAN, M. DOOLEY, and K. WORKING, *Use of a Radiotherapy Treatment Planning Computer for Dosimetry of the AFRRI Cobalt-60 Facility*, Technical Report TR 84-5. Armed Forces Radiobiology Research Institute, Bethesda, MD, 1984.